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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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10/511,452

10/14/2004

Paul Leslie Ornstein

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11/08/2006

ELI LILLY & COMPANY

PATENT DIVISION

P.O. BOX 6288

INDIANAPOLIS, IN 46206-6288

EXAMINER

SEAMAN, D MARGARET M

ART UNIT

PAPER NUMBER

1625

DATE MAILED: 11/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/511,452

Applicant(s)

ORNSTEIN, PAUL LESLIE

Examiner

D. Margaret Seaman

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 41-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application was filed 14 October 2004 and is 371 of PCT/US03/10466 (4/14/2003) which claims benefit of Provisional Application 60/376120 (4/26/2002). RCE papers were filed 10/25/2006. Claims 1-20, 22-23 and 26-40 were canceled. Claims 41-60 are before the Examiner.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

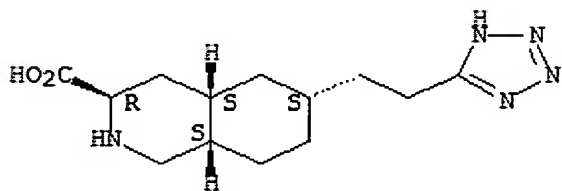
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 41-60 are/rejected under 35 U.S.C. 103(a) as being unpatentable over Salhoff in view of Bundgaard (WO 8801615) and Wang (Current Med Chemistry, Vol 7,, pp437-453, 2000). The rejection is maintained. As previously stated:

Salhoff teaches compounds such



as

that are useful to treat pain. Salhoff does

not teach the ester on the three position of the isoquinoline core.

Bundgaard teaches that ester derivatives of known compounds are prodrug formulations of carboxylic acid drug and provide improved bioavailability and are less irritating to the mucosa. Wang teaches that prodrug technology has improved to include simple ester prodrugs, double prodrugs among others that improve membrane permeability and activity.

It would have been obvious to one of ordinary skill in the art to take a known drug, such as the above shown decahydroisoquinoline, and make a simple ester prodrug formulation with the reasonable expectation of getting a prodrug having better capabilities than the parent drug. Rationale: Bundgaard teaches the ester formulations of carboxylic acid drugs. Wang teaches simple ester prodrugs improve the prodrug technology since 1993 and Salhoff teaches the compound as a valuable drug.


Applicant continues to argue that Bundgaard does not teach the use of the smaller ester prodrug formulations and that Bundgaard actually teaches away from the instant invention. Now, further in view of Wang that teaches the development of prodrug technology, that simple ester prodrugs among others, improve membrane

permeability and oral activity. However, Bundgaard teaches any and all ester prodrug formulations but has specific examples of the larger prodrug formulations. To show that the ordinary artisan knows of the smaller ester prodrug formulations, are Bundgaard (J of Med Chem, Vol 28, Number 8, August 1985, pp 979-981) that has alkyl and aralkyl esters of pilocarpic acid to correct a delivery problem with the original drug and Wang (Current Med Chem, Vol 7, pages 437-453, 2000) which makes simple ester prodrugs such as methyl and ethyl prodrugs to improve membrane permeability and oral activity. Bundgaard and Wang show that even the small prodrug formulations are known in the art of prodrug formulations as is taught by Bundgaard (WO 8801615). Simple ester prodrug formulations are well known in the art as further shown by Bibby, Kao, Stinchcomb and Doh.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


D. Margaret Seaman
Primary Examiner
Art Unit 1625

dms